

Voxel based morphometry analysis of anti-retroviral effects in early HIV infection

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Background: Antiretroviral therapy (ART) has reduced AIDS-related deaths worldwide¹; however, neurocognitive impairment is evident in nearly 50% of patients receiving treatment². This may reflect limited penetration of ART through the blood brain barrier resulting in reduced treatment efficacy in the central nervous system. The neuroprotective benefit of ART, therefore, is not well characterized. Evidence suggests that some agents used in ART regimens may actually be neurotoxic^{3,4}. In order to assess the effects of treatment on the brain, this study used voxel based morphometry (VBM) to compare gray matter volume in treated and untreated HIV+ subjects and age matched controls.

Methods: Fifty recently infected HIV+ (25 treated, 25 treatment naïve) and 20 age-matched control participants were enrolled and gave IRB-approved informed consent. Recency of infection in the HIV+ subjects was determined using an early infection assay (Blood Systems, San Francisco, CA). Magnetization prepared rapid acquisition gradient echo (MP-RAGE) was acquired at 3T [TR/TI/TE=2300/900/2.91ms, flip angle=9°, field of view=256x256mm, slice thickness=1mm, in-plane resolution=1mm isotropic; slices=176]. VBM analysis of gray matter was performed in Statistical Parametric Mapping (Wellcome Trust, London, UK) using analysis of variance (ANOVA). A voxel was considered significant if $p < 0.005$ and if it belonged to a Family-Wise Error corrected cluster ($p < 0.05$). The analysis co-varied for age and the total cranial volume was included as a global nuisance variable.

Results: The HIV (32.6 ± 9.6 years) and control (31.8 ± 8.9 years) groups did not differ significantly in age ($p = 0.75$) or in educational status ($p = 0.74$). Based on assay values, the HIV cohort was estimated to be infected less than one year on average and the length of infection did not differ in ART naïve and treated HIV subgroups ($p = 0.27$). When compared to controls, the HIV+ group ($n = 50$) had significantly ($p < 0.005$) less gray matter volume, with prominent changes noted in insular cortex. The HIV+ subgroup on ART ($n = 25$) showed significant volume reductions ($p < 0.005$) in insular cortex, as well as medial frontal and orbital frontal cortex compared to controls. However, regions of gray matter volume reduction in the treatment naïve HIV+ subgroup ($n = 25$), while significant in uncorrected analysis, did not pass the false discovery rate correction. Further direct comparison of the naïve vs. treated HIV+ subgroups (*Figure 1*) indicated significantly ($p < 0.005$) reduced gray matter volumes in anterior cingulate, insular cortex, precuneus, temporal gyrus and temporal pole in the treated subjects.

Conclusions: Reduction in gray matter is observed in the first year of HIV infection. While treated and untreated HIV subgroups did not differ in length of infection, gray matter reduction was more prominent in subjects who had initiated treatment than in those who were treatment naïve. These findings suggest possible treatment toxicity and/or injury related to immune reconstitution. Further studies are needed to explore how these early changes evolve over time and their prognostic significance for long term neurologic outcome.

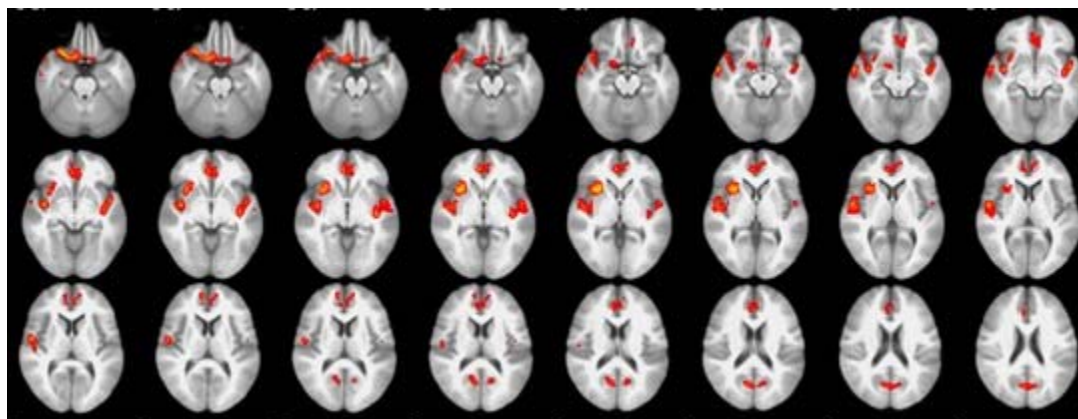


Figure 1: Regions of gray matter volume reduction (red) in the treated group compared to the naïve group displayed on the composite structural image.

- References** 1. UNAIDS Report on the Global Aids Epidemic. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2010. 2. Heaton RK, Clifford DB, Franklin DR Jr, et al. Neurology 2010; 75(23): 2087-2096 3. Clifford DB. Neurology 2010;74(16):1248-1249. 4. Robertson, K. R., Z. Su, et al. (2010). Neurology 74(16): 1260-1266.